

Diabetes UK Position Statements

Improving understanding of type 2 diabetes remission: research recommendations from Diabetes UK's 2019 remission workshop

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Abstract

Aim To describe the process and outputs of a workshop convened to identify key priorities for future research in the area of remission of type 2 diabetes, and provide recommendations to researchers and research funders on how best to address them. With the ultimate aim of enabling the remission of type 2 diabetes to become a possibility for more people.

Methods A 1-day research workshop was conducted, bringing together 31 researchers, people living with diabetes, healthcare professionals and members of staff from Diabetes UK to identify and prioritize recommendations for future research into remission of type 2 diabetes.

Results Workshop attendees identified 10 key themes for further research. Four of these themes were prioritized for further focus: (i) understanding how to personalize lifestyle approaches based on biology, patient choice and subtypes; (ii) understanding the biology of remission; (iii) understanding the most effective approaches to implementation of lifestyle interventions; and (iv) understanding the best approaches to combining therapies (gut hormones, other drugs, lifestyle approaches and bariatric surgery).

Conclusions This paper outlines recommendations to address the current gaps in knowledge related to remission of type 2 diabetes.

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Introduction

Can type 2 diabetes be cured or reversed, what is the best way to achieve this and is there a point beyond which the condition can't be reversed?

This was the number one priority raised by people with type 2 diabetes and healthcare professionals, as part of the type 2 diabetes James Lind Alliance Priority Setting Partnership – involving insight from over 4000 people [1].

It has been known for a number of decades that remission of type 2 diabetes is possible [2], with bariatric surgery resulting in remission of hyperglycaemia in 30–60% of cases [3]. However, access to bariatric surgery is limited, meaning that only a relatively small number of people with type 2

diabetes currently access this treatment. Recent evidence has also emerged showing that lifestyle interventions can induce and maintain type 2 diabetes remission. The Diabetes Remission Clinical Trial (DiRECT) demonstrated that 10–15% weight loss after a low-calorie weight management programme delivered through primary care can lead to remission for at least 2 years in 36% of people [4] but low calorie weight management programmes are not as yet routinely available within the UK National Health Service (NHS).

As therapies become more commonly available, to ensure that as many people as possible can benefit from these approaches there is a need to both clearly define remission and for research to further our understanding of remission and what it means for people with type 2 diabetes.

The Association of British Clinical Diabetologists (ABCD) and the Primary Care Diabetes Society (PCDS) have published a consensus statement defining remission based on

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What's new?

- It is known that type 2 diabetes can be put into remission; however, standard clinical treatment of type 2 diabetes does not currently aim to put the condition into remission.
- This is the first time that researchers and healthcare professionals from a wide range of specialist areas have come together to identify research priorities to increase understanding of remission of type 2 diabetes.
- The paper sets out key recommendations for further research that is needed in order to make remission an achievable aim for more people with type 2 diabetes.

three criteria: (i) weight loss, (ii) $\text{HbA}_{1c} < 48 \text{ mmol/mol}$ (6.5%) on two occasions with at least a 6-month interval between them, and (iii) cessation of all glucose-lowering therapies [5]. Work is also ongoing between the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD) and Diabetes UK to agree an international consensus definition for type 2 diabetes remission.

To further enhance our understanding of remission of type 2 diabetes, Diabetes UK convened a workshop with the aim of identifying priorities for future research.

Methodology

In July 2019, Diabetes UK brought together diabetes clinical studies group (CSG) members and experts from a variety of backgrounds, including people living with type 2 diabetes, for a 1-day workshop to identify the key gaps in evidence and priority research questions in the area of type 2 diabetes remission. In total, there were 31 attendees, including four people living with diabetes, 20 researchers and healthcare professionals, and five members of staff from Diabetes UK who facilitated the workshop. Attendees are listed in Appendix S1.

The workshop format began with three presentations from experts in the field. These presentations provided an overview of current evidence related to remission of type 2 diabetes in relation to lifestyle interventions (Professor Roy Taylor), bariatric surgery (Professor Carel le Roux) and gut hormone research (Dr Victoria Salem).

After each presentation, attendees were organized into the same group of six or seven, with representation from different specialities and a person with or in remission of type 2 diabetes, and were asked to discuss and answer three questions: (i) where are the current areas of strength in existing research evidence; (ii) how can this evidence be built on; and (iii) where is further evidence needed?

Each group was asked to identify one or two priorities for further research. In total, around 40 research priorities were

identified. The Diabetes UK facilitation team then clustered these priorities into 10 themes:

- How can lifestyle interventions be personalized, based on biology, individual choice and variation?
- Can we better understand the biology of remission (e.g. why responses differ, how these differences could be measured)?
- How can lifestyle interventions be implemented most effectively (including approaches to weight loss and maintenance, scalability, and models of delivery)?
- Who is most likely to benefit from bariatric surgery (e.g. could biomarkers be used to predict response) and when should it be offered?
- What is the psychological impact of bariatric surgery, remission and no longer being in remission (including use of language)?
- Is bariatric surgery an effective way to reach remission in young people with type 2 diabetes?
- What are the factors affecting access to bariatric surgery (considering both the barriers and enablers, as well as the impact of stigma)?
- How and where do gut hormones work (including their safety profiles and effects on other organs)?
- How could gut hormone therapy be personalized (e.g. could genetics be used to predict response)?
- What are the best approaches to combining therapies (gut hormones, other drugs, lifestyle approaches and bariatric surgery)?

In order to focus discussions further, each workshop attendee was asked to vote for their top three themes, the results of this vote can be seen in Table S1.

Following this voting exercise, the top five themes were identified and attendees were individually asked to choose the theme they wished to focus on for the remainder of the workshop. One theme—understanding who will benefit most from bariatric surgery—was not prioritized because no workshop attendees chose it as an area for further discussion. The four themes which were prioritized for in-depth discussion were:

1. Understanding how to personalize lifestyle approaches based on biology, patient choice and subtypes.
2. Understanding the biology of remission.
3. Understanding the most effective approaches to implementation of lifestyle interventions.
4. Understanding the best approaches to combining therapies (gut hormones, other drugs, lifestyle approaches and bariatric surgery).

Each group was asked to discuss three questions: (i) what are the research questions; (ii) what approaches could be taken to answer these questions; and (iii) what are the barriers to this research and how could they be overcome?

Each group was asked to feedback on their discussions, and other attendees had the opportunity to input thoughts and ideas. All discussions were captured to inform this paper.

This paper provides a summary of these discussions and the key research priorities that were identified in order to advance our understanding of remission of type 2 diabetes. We note that some of the priorities outlined move beyond the scope of the themes; however, they do represent the output of these discussions.

Research priorities and recommendations

Theme 1: Understanding the biology of remission

β-Cell function

Findings from DiRECT indicate that significant weight loss can result in a reduction in the levels of fat within the pancreas and liver [6], and in turn, improve β-cell function [7]. However, a small number of DiRECT participants who lost significant weight did not go into remission; reduced levels of fat within their pancreas and liver did not result in improved β-cell function. Further research is needed to understand the reasons behind these differences, and the potential need for stratification in future remission programmes.

Mechanisms behind bariatric surgery

There are a number of different bariatric surgery procedures and current evidence suggests that these can lead to the remission of type 2 diabetes in 30–60% of people [3]. However, evidence also suggests that 35–50% of people who initially go into remission will experience recurrence of the condition [3]. A recent population study of type 2 diabetes remission rates following Roux-en-Y gastric bypass (RYGB) surgery found that 73% of people in remission at 12 months were still in remission at 5 years [8]. The study also identified potential predictive factors for not achieving remission, such as age > 50 years, diabetes duration of > 5 years, use of glucose-lowering medication other than metformin, and a baseline HbA_{1c} > 53 mmol/mol (7.0%).

Bariatric surgery was noted to enhance levels of postprandial satiety gut hormone responses, leading to reduced appetite and food intake [9]. Changes to gut hormone levels have been suggested as one of the mechanisms responsible for improvements in glycaemic control after surgery, particularly before significant weight loss has occurred [10], and the gut hormone incretin glucagon-like peptide 1 (GLP-1) has already been developed into treatments for type 2 diabetes and obesity. Dual treatment with GLP-1 and glucagon has been shown to significantly reduce food intake compared with monotherapy [11], and improve bodyweight, fasting

glucose and glucose tolerance [12]. A separate small study into the use of a triple agonist (GLP-1, oxyntomodulin and peptide YY) replicated the gut hormone responses seen post-RYGB and led to reduced food intake, albeit not to the same magnitude as surgery itself, and normalized glycaemic control [13].

However, gut hormones may not be the only factor behind normalization of glycaemic control after bariatric surgery [14], given that reduced calorie intake—whether through diet alone or bariatric surgery—can bring about normalization of glycaemic control after 7 days, with the underlying mechanisms shown to be the same [15,16]. Decreased food intake brings about marked normalization of hepatic fat content and hepatic insulin sensitivity, and these factors are capable of decreasing the output of glucose from the liver and decreasing fasting plasma glucose [15–17].

As such, further research is needed to explore how combination hormone therapies could be used to aid weight loss, promote weight loss maintenance, augment glycaemic control and improve health outcomes in the future.

Predicting responses

The potential use of biomarkers to provide more personalized diabetes treatment is of increasing interest [18]. A greater understanding of the biomarkers that could be used to predict responses to remission interventions would also be beneficial, to support people with type 2 diabetes and healthcare professionals to make informed choices about the most appropriate treatment plans and clinical pathways.

Research priorities

The group recommended that further research is needed to build a greater understanding of:

- the biology of β-cell recovery, to stratify and target future remission interventions;
- the role of gut hormone therapy in remission, particularly building on initial small-scale studies; and
- novel biomarkers which could be used to predict response to remission interventions in the future.

Theme 2: Understanding how to personalize lifestyle approaches based on biology, individual choice and variation

Evidencing different lifestyle interventions

In order to make remission a reality for as many people with type 2 diabetes as possible, we are likely to need a variety of lifestyle interventions, to meet the physiological, psychological and cultural needs of each individual. Further research to develop a rigorous evidence-based suite of options would improve individual choice and personalization.

Currently, the strongest evidence of remission exists for the use of a low-calorie weight management programme and bariatric surgery [3,4].

Some industry-funded studies have also suggested that low-carbohydrate diets may result in remission for some people (17.6% of participants were in remission 2 years post intervention initiation) [19], and there are many self-reported cases of remission using this approach. More rigorous research is required to build evidence in this area, in order to influence clinical practice, and a number of research questions around the effects of low-carbohydrate diets were identified:

- What constitutes a low-carbohydrate diet?
- Can a low-carbohydrate diet restore normal glucose and insulin metabolism and achieve remission of type 2 diabetes in the long-term?
- What is the long-term impact of a low-carbohydrate diet on other aspects of health, particularly the effects of relatively increasing or decreasing other macronutrients; for example, lipids on cardiovascular outcomes or protein on kidney function?
- Could a low-carbohydrate diet be used to support people to maintain weight loss after other dietary approaches?
- Do low-carbohydrate diets provide additional health benefits for people with type 2 diabetes, or people in remission, beyond weight loss?

Effective approaches for people of different ethnicities

There is a current gap in evidence regarding the effectiveness of low-calorie weight management programmes in people of different ethnicities. DiRECT participants were largely representative of the local populations in the trial areas, but they were predominantly white [4]. There is a need to identify effective lifestyle approaches to remission for people from black, Asian and minority ethnic (BAME) populations, and this will involve a more in-depth understanding of both physiological and cultural factors which may affect effectiveness. For example, preliminary research has suggested that the biology underlying the development of type 2 diabetes may differ in black African men, suggesting that more tailored prevention or remission options may be required [20]. However, initial findings from a recent feasibility study in a small group of people who were predominantly black suggest that a low-calorie diet could be effective in restoring normal glucose and insulin metabolism [21].

Research priorities

The group recommended that further research is needed to build a greater understanding of:

- the role of low-carbohydrate diets in remission, particularly through robust clinical trials; and
- the effectiveness of different lifestyle interventions in different BAME communities, requiring more diverse representation in future studies.

Theme 3: Understanding the most effective approaches to implementing interventions

Meeting local and national needs

To ensure that more people can achieve remission of type 2, local and national health services will need to begin to offer effective, remission services.

In the UK, the NHS has responded to the latest evidence around low-calorie weight management programmes, with rapid moves to begin implementation of such programmes within the NHS. The NHS in England has begun planning a pilot programme for ~ 5000 people with type 2 diabetes [22], and commissioners within a number of local health economies in England have begun to commission and procure remission programmes. The NHS in Scotland has also begun to roll out remission programmes in some parts of the country [23].

There are a number of challenges in translating research into clinical practice. Within the UK, there is significant variation in how the NHS is organized at a national, regional and local level, as well as competing demands for funding and workforce capacity. Against this backdrop, there will be a desire to find ways of adapting evidence-based programmes to meet local circumstances. For example, changes could include the use of group-based consultations, digital platforms or remote interventions.

As such, evaluations of how these changes could impact the efficacy and cost-effectiveness of such programmes is needed, to inform future commissioning decisions. Some studies exploring different options are now underway [24].

Research exploring the effectiveness of the implementation of these interventions will provide useful evidence both to the UK and for other health systems internationally as they consider their approaches to treat type 2 diabetes.

Maintaining weight loss

Evidence suggests that maintaining weight loss after a lifestyle intervention is key to long-term remission, with significant weight gain resulting in the re-emergence of type 2 diabetes [3]. A large number of studies have investigated the effectiveness of behaviour change interventions, but there is limited research into the sustainability of behaviour change after the intervention phase ends [25]. Therefore, further research is needed to identify evidence-based approaches to supporting people to maintain weight loss.

DiRECT demonstrated that intensive support in participants who regained some weight, through an optional 'rescue protocol' involving a further short period of low-calorie meal replacements, was effective in supporting some people to stay in remission at 24 months [4]. Questions remain regarding the practicality of offering repeat 'rescue' packages within normal clinical practice. Research into the efficacy and cost-effectiveness of the long-term use of 'rescue' packages, compared with one-off upfront interventions, to support

weight maintenance would help to support the effective implementation of ongoing support to maintain weight loss.

Further research to identify effective approaches for supporting people to maintain weight loss, and therefore potentially remain in remission, in the long term is now needed. This includes research to build our understanding of the role of physical activity, both in weight loss and long-term weight maintenance. Greater collaboration between researchers working in the fields of diet, physical activity and psychology could be beneficial to support this.

Acceptability and wider long-term impact

With the concept of remission being relatively novel, there is now a need to better understand how its introduction into the diabetes field has affected both research study designs and care pathways, and this will require insight from people with type 2 diabetes and healthcare professionals.

Further research into the psychological effects of remission is also required, including research to establish the impact of re-emerging type 2 diabetes, significant dietary changes during weight loss, and the potential risks of developing disordered eating.

The number of people who receive bariatric surgery in the UK is lower than most other European countries [26]. Research is needed to identify the barriers preventing greater uptake of bariatric surgery and ways to overcome them. This would need to involve an exploration of the views of people with type 2 diabetes, healthcare professionals and the wider public, the political and commissioning challenges that limit funding, and the clinical pathways for surgery.

Research priorities

The group recommended that further research is needed to build a greater understanding of:

- the impact of different delivery models of lifestyle interventions on their efficacy in real-world settings;
- the health economic implications of remission interventions;
- evidence-based approaches to maintaining weight loss, including the role of physical activity and the efficacy and cost-effectiveness of 'rescue' packages within lifestyle interventions;
- the psychological impact of each aspect of remission, including on those people who are not able to go into remission;
- barriers to the greater uptake of bariatric surgery.

Theme 4: Understanding the best approaches to combining therapies (gut hormones, other drugs, lifestyle approaches and bariatric surgery)

Individually, hormone therapies, lifestyle interventions and bariatric surgery have all been shown to support

improvements in blood glucose levels, with the possibility of putting type 2 diabetes into remission for some.

As understanding of the underlying biology of remission improves, there could be potential in exploring the efficacy of combination therapies to enable a significant reduction in blood glucose levels to put type 2 diabetes into remission and maintain this in the long term. There are a range of combinations which could be tested. For example, given the importance of weight loss maintenance in sustaining remission following lifestyle interventions, post-intervention hormone therapies could potentially be used to support weight maintenance.

Further research into the efficacy and cost-effectiveness of different combination therapy approaches needs to be established. For example, in the case of type 2 diabetes remission, health funders may be motivated by both improved health outcomes and the potential to reduce spending on high-cost drugs. The cost implications of introducing hormone therapies to maintain remission would therefore need to be explored.

Further research is also needed to align potential combination therapy options with the variation within type 2 diabetes, through an increased understanding of how to effectively stratify people living with the condition. In the future, this could enable healthcare professionals to target more aggressive combination therapies to people at greatest risk of progression to complications.

Research priorities

The group recommended that further research is needed to build a greater understanding of:

- the potential of combination interventions and therapies, including their efficacy and cost-effectiveness; and
- how to effectively stratify type 2 diabetes and align remission interventions with the individual.

Collaboration and involvement

Workshop discussions highlighted the significant interest in understanding remission among the research community, with many people already working within the field. One of the messages repeated throughout the day by different people was that greater collaboration among researchers would benefit the field in making further progress.

Large-scale trials involving high numbers of participants are needed to answer some of the questions within this paper. Although this presents significant challenges, including funding, there is the opportunity and potential to embed relevant research in large-scale health programmes. Greater collaboration between health systems and the research community could lead to greater advances in our understanding of remission, and ultimately lead to more people in remission of type 2 diabetes.

Conclusion

How to put type 2 diabetes into remission is the most important research question for people living with the condition [1]. The research community has made great strides in making remission a possibility for some people with type 2 diabetes, but as this paper sets out, many more questions remain to be answered.

Diabetes UK has identified remission of type 2 diabetes as a key strategic priority for the years ahead [27]. Addressing the recommendations for future research set out within this paper, in collaboration with researchers, funders, health services and people with diabetes, will enable us to make remission of type 2 diabetes a reality for as many people as possible.

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Competing interests

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Workshop attendees who have agreed for their names to be included.

Table S1. Results of the vote to choose the top five priorities from the 10 research themes identified during the first session of the workshop.